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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/687,401	10/13/2000	Ian David Manger	20174-002300US	9512

20350 7590 02/25/2004

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EXAMINER	
SODERQUIST, ARLEN	
ART UNIT	PAPER NUMBER
1743	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/687,401	Applicant(s) MANGER ET AL.
	Examiner Arlen Soderquist	Art Unit 1743

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 21 November 2003.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,4,6-10,14-24,28-31,33-45 and 49-59 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,4,6-10,14-24,28-31,33-45 and 49-59 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 21, 2003 has been entered.

2. Claims 1, 4, 6-10, 14-24, 28-31, 33-45 and 49-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 1, lines 5-6 "said second elastic layer" does not have antecedent basis since the terms are different. For examination purposes the phrase will be treated as "said second elastomeric layer". In subparagraph (c) of claim 1 it is not clear which elastomeric layer contains the fluid flow channel since there are two different layer s that are claimed. Additionally in claim 1 sub paragraph (b) there are two different elements -- a pump and valve system and a pressure channel -- that the second layer is supposed to comprise yet there is no structural connection provided between them. It is not clear if there is a structural connection between the two elements or if applicant is trying to define the second elastomeric layer as two different things. For examination purposes examiner will treat the language as including structural connections between the two elements (the structure of the Unger reference meets this structural connection). Claim 14 is dependent from a canceled claim and "said sample interface means" does not have antecedent basis in any claims which are dependent from claim 1. Claim 15 is dependent from a canceled claim. In claims 18, 31 and 37, the structural connection between the pressure channel and the pump and valve system is not clear. In the specification it appears that the pressure channel is an element of the pump and valve system, but the claim provides no structural connection. In claim 49, "said sample preparation chamber" does not have antecedent basis in claim 37. In claim 52, there appears to be a grouping that is improperly listed. It should either have the Markush format or the elements should be listed in the alternative. In claim 58, it is not clear if the plurality of sample preparation chambers is in addition to the one of claim 45 or if the plurality of sample preparation chambers is lacking a structural connection with the other elements of the device.

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

2. Claims 1, 4, 6-10, 14-24, 28-31, 33-45 and 49-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger in view of Chan and Duffy, Figeys (either 1998 Analytical Chemistry article), Parce (US 5,885,470), Ullman or Xue (1997) and Ericson (newly cited and applied). In the paper Unger discusses monolithic microfabricated valves and pumps by multilayer soft lithography. Soft lithography is an alternative to silicon-based micromachining that uses replica molding of nontraditional elastomeric materials to fabricate stamps and microfluidic channels. They describe an extension to the soft lithography paradigm, multilayer soft lithography, with which devices consisting of multiple layers may be fabricated from soft materials. They used this technique to build active microfluidic systems containing on-off valves, switching valves, and pumps entirely out of elastomer. The softness of these materials allows the device areas to be reduced by more than two orders of magnitude compared with silicon-based devices. The other advantages of soft lithography, such as rapid prototyping, ease of fabrication, and biocompatibility, are retained. The primary material discussed is polydimethylsiloxane for producing the devices and structures. Figure 1 shows the manufacturing process including making two layers having different ratios of monomers in order to bond the layers together. This is described in the paragrapgh bridging columns 2-3 on page 113. Also in that paratraph is the teaching that the bonding process produces a hermetic seal. Figure 2 shows different valve and pump configurations made. Figure 4 shows how the peristaltic pump works. The figures also give dimensions that are within the claimed ranges. The last full paragraph on page 113 teaches that the all elastomer valves and pumps avoid several

practical problems of electroosmotic and electrophoretic flow in microfluidics devices. In the first paragraph of page 116 the use of these valves in a wide variety of lab on a chip applications is predicted. The Unger reference does not give specific structure for those devices.

In the paper Chan teaches microfabricated polymer devices for automated sample delivery of peptides for analysis by electrospray ionization tandem mass spectrometry. Delivery of proteins and peptides to electrospray ionization mass spectrometers (ESI-MS) has been demonstrated using glass and quartz microfabricated devices. This paper reports the construction and use of poly(dimethyl-siloxane) (PDMS) microfabricated soft polymer devices with mass spectrometry for protein analysis. The PDMS devices were fabricated using replica molding against a patterned photoresist generated by photolithography techniques. The PDMS devices were connected to the mass spectrometer via a derivatized transfer capillary and samples were transferred by electro-osmotic pumping. The formulation of PDMS was optimized for compatibility with ESI, and the devices were tested for performance. The practical application of PDMS devices was demonstrated by the identification of rat serum albumin separated by 2-D gel electrophoresis. Extended contact of the sample with the surface of the PDMS device did not significantly affect the sample analysis, and the limit of detection for samples run on a PDMS device was comparable to the limit of detection achieved on glass devices. This study suggests that PDMS devices fabricated using replica molding are compatible with ESI-MS. This will potentially lead to the construction of inexpensive microfabricated devices with complex designs and advanced functionalities. The channel has a width of 75 μm (page 4438).

In the paper Duffy teaches the preparation of microfluidic systems in polydimethylsiloxane. This paper describes a procedure that makes it possible to design and fabricate (including sealing) microfluidic systems in an elastomeric material-poly(dimethylsiloxane) (PDMS)-in less than 24 hours. A network of microfluidic channels (with width >20 μm) is designed in a CAD program. This design is converted into a transparency by a high-resolution printer; this transparency is used as a mask in photolithography to create a master in positive relief photoresist. PDMS cast against the master yields a polymeric replica containing a network of channels. The surface of this replica, and that of a flat slab of PDMS, are oxidized in an oxygen plasma. These oxidized surfaces seal tightly and irreversibly when brought into conformal contact. Oxidized PDMS also seals irreversibly to other materials used

in microfluidic systems, such as glass, silicon, silicon oxide, and oxidized polystyrene; a number of substrates for devices are, therefore, practical options. Oxidation of the PDMS has the additional advantage that it yields channels whose walls are negatively charged when in contact with neutral and basic aqueous solutions; these channels support electroosmotic pumping and can be filled easily with liquids with high surface energies (such as water). The performance of microfluidic systems prepared using this rapid prototyping technique has been evaluated by fabricating a miniaturized capillary electrophoresis system. Amino acids, charge ladders of positive and negative charged proteins, and DNA fragments were separated in aqueous solutions with this system with resolution comparable to that obtained using fused silica capillaries.

In the two sequential 1998 Analytical Chemistry articles Figeys teaches integrated microfluidic devices for protein analysis and identification in which the microfluidic device is connected to an electrospray ionization mass spectrometer.

In the patent Parce teaches controlled fluid transport in microfabricated polymeric substrates. Microfluidic devices are provided for the performance of chemical and biochemical analyses, syntheses and detection. The devices of the invention combine precise fluidic control systems with microfabricated polymeric substrates to provide accurate, low cost miniaturized analytical devices that have broad applications in the fields of chemistry, biochemistry, biotechnology, molecular biology and numerous other fields. Column 5 lines 52-67 teach various polymeric materials including PDMS. Column 12 line 65 to column 13 line 30 teaches the variety of uses for the microfluidic devices including immunoassays.

In the patent Ullman teaches capillary assays involving the separation of free and bound species. The invention concerns methods for masking inhomogeneity of a member of a specific binding pair (sbp) employed in a capillary electroseparation. The method comprises binding the sbp member to synthetic particles that become localized during capillary electroseparation. Also disclosed is one embodiment of the present invention, which is a method for conducting a capillary electroseparation specific binding assay. The method involves the electroseparation of a labeled first member of a specific binding pair that is bound in a complex from labeled first member that is not bound in the complex. The complex comprises the first member and a second member of a specific binding pair. A combination is provided comprising a sample suspected of containing an analyte, a labeled first member of a specific binding pair, and a second member of

a specific binding pair under conditions for forming a complex between labeled first member and the second member. The second member either initially or subsequent to the formation of the complex being covalently or noncovalently bound to synthetic particles that migrate uniformly during electroseparation. The combination is subjected to electroseparation and a determination is made as to whether the complex is formed. Also disclosed are kits for conducting a capillary electroseparation specific binding assay. Columns 6-11 teach various things that can be used including enzymes and cells.

In the paper Xue teaches an integrated multichannel microchip electrospray ionization mass spectrometry: analysis of peptides from on-chip tryptic digestion of melittin. In continuation of their work to develop an integrated multichannel microchip interface to electrospray mass spectrometry (ESI-MS), the paper demonstrates one of several applications of this approach in monitoring tryptic digestion products. The multichannel microchip allowed integration of sample preparation onto the microchip to facilitate the analytical process. Melittin was selected as a model oligopeptide because it possesses a cluster of four adjacent basic residues which enable probing the site specificity of trypsin as a function of digest times. Reactions were performed on-chip in different wells for specific time periods and then analyzed by infusion from the microchip by ESI-MS, using leucine-enkephalin as internal standard. The rate of formation and disappearance of the molecular ion and individual fragments was followed for a melittin-to-trypsin concentration ratio of 300:1. The results indicate the potential of integrating enzymic reactions with multichannel microchip ESI-MS for automated optimization of reaction conditions while consuming only small amounts of sample.

In the papper Ericson discusses electroosmosis- and pressure-driven chromatography in chips using continuous beds. The application range of microchips can be extended to any mode of chromatography by filling the narrow channels with continuous polymer beds, exemplified by electrochromatography and ion-exchange chromatography. Wall effects are eliminated by anchoring the bed to the wall of the channel, an arrangement which has the additional advantage that no frits to support the bed are required. The design of the equipment is based on a quartz chip with all auxiliary pieces (for example, electrode vessels and fluid transfer fittings) placed in a rack, which permits a flexibility of great importance for automation. The same resolution and van Deemter plots were obtained in experiments performed in fused-silica capillaries and in

chips for both low-molecular-weight (alkyl phenones, antidepressants) and high- molecular-weight substances (proteins). A sample of uracil, phenol, and benzyl alchohol was separated by electrochromatography in <20 seconds.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate different components of analytical devices and sample modification means taught by Duffy, Chan, Figeys, Parce, Ullman or Xue into the Unger structure because of their known use and benefits in microfluidic devices for analysis of samples in particular as shown by Chan and the advantages taught by Unger for the elastomeric pumps and valves regarding the fluid flow in microfluidic devices. Furthermore the Ericson paper clearly shows that both types of fluid flow are known in microfluidic devices and thus one of skill in the art would have been capable of adapting the structures of one type of device using electroosmotic pumping to a second type of device using pumps to provide the fluid flow in the device.

3. Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection. The Unger reference clearly teaches the instantly claimed pumps and valves and their use in a variety of microfluidic applications. The Ericson reference clearly shows that fluid flow in microfluidic device is known to include that caused by pumps.

4. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The additionally cited art relates to fluid transfer in capillary and microfluidic devices.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose current telephone number is (571) 272-1265 as a result of the examiner moving to the new USPTO location. The examiner's schedule is variable between the hours of about 5:30 AM to about 5:00 PM on Monday through Thursday and alternate Fridays.

A general phone number for the organization to which this application is assigned is (571) 272-1700. The fax phone number to file official papers for this application or proceeding is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 19, 2004

ARLEN SODERQUIST
PRIMARY EXAMINER